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Abstract

Purpose of review. The aim of the present manuscript is to provide an overview of the most updated studies on the prevalence of primary aldosteronism in primary care and to compare these figures with the actual rate of diagnosis in clinical practice and with the prevalence of PA in specific subgroup of patients.

Recent findings. Over the last 20 years the clinical spectrum of low renin hypertension and primary aldosteronism has changed dramatically. Once considered only in the presence of severe hypertension and hypokalemia, it is now well known that PA is not uncommon even in patients with mild forms of hypertension and/or normokalaemia. Moreover, recent evidence points towards a large proportion of

normotensive subjects as being affected by subclinical PA, which represents a strong risk factor for incident hypertension. Moreover, PA patients are exposed to an increased risk of cardio- and cerebro-vascular events and metabolic comorbidities compared with patients affected by essential hypertension. Disappointingly, primary aldosteronism remains a largely underdiagnosed and under-treated disorder.

Summary. These recent findings further highlight the importance of widening the spectrum of patients who should be screened for PA, to reduce the cardiovascular risk associated with this medical condition.

Key words: aldosterone, primary aldosteronism, aldosterone producing adenoma, bilateral adrenal hyperplasia, primary care

Introduction

The 2016 *Lancet* commission on hypertension highlighted that missing a diagnosis of secondary hypertension is one of the most important reasons for the unacceptably low control rate of blood pressure levels in patients with hypertension [1]. Although the 2016 Endocrine Society (ES) guideline suggests screening for primary aldosteronism (PA) all patients with hypertension and high risk of PA, [2**], which account for more than half of the hypertensive population, the diagnosis of PA is still largely inadequate [3*].

Recently, the PATO (primary aldosteronism in Torino) study reported a PA prevalence of about 6% in a large cohort of unselected patients with hypertension referred by general practitioners (GPs). PA prevalence increased with the severity of hypertension, but notably 44% of the identified cases were affected by stage I hypertension (that is systolic blood pressure level comprised between 140-160 mmHg and/or diastolic levels comprised between 90-100 mmHg) [4*]. These data are particularly relevant for the observed significant association between PA and a higher risk of cerebro- and cardio-

vascular events, cardiac organ damage and metabolic comorbidities compared with patients with essential hypertension, independent of blood pressure levels [5*]. In fact, the identification of patients with PA and a correct subtype diagnosis are important to offer a prompt and specific treatment (surgical cure or targeted pharmacotherapy) which has been demonstrated not only to significantly improve blood pressure and correct electrolyte abnormalities [6*,7**], but even to revert target organ damage [8,9] and reduce the cardiovascular associated risk [7**].

Prevalence of primary aldosteronism among patients with hypertension

Over the last 25 years many studies investigated the prevalence of PA in primary care settings and in referral centres. Although diagnostic criteria varied widely between different studies, especially in those performed before the publication of the first ES Guideline in 2008 [10], a median PA prevalence of around 6% in primary care setting and 11% in referral centres is observed [11].

Prevalence of PA in primary care progressively increases with the severity of hypertension, from 2-4% in mildest forms to 12-13% in the most severe forms, [4*,12] and from 7% in mildest forms to 19% in the most severe in referral centres [13]. In patients with resistant hypertension, PA reaches its highest prevalence (up to 20%) [14].

A correct subtype diagnosis allows the identification of an aldosterone producing adenoma (APA) in one third of PA cases and bilateral adrenal hyperplasia (BAH) in the remaining patients [4*,15]. Hypokalaemia, once considered a prerequisite to screen for PA, is observed in only 25-40% of patients with confirmed PA [4*,11,15], and more frequently in patients with resistant hypertension (45-70%) [16].

PA seems to be more prevalent in some specific subgroups, such as patients with hypertension and obstructive sleep apnoea syndrome (OSAS) [17]: for this reason, the 2016 Guideline recommends that PA screening should be extended also to this category of patients [2*].

The association between PA and a higher risk of developing type 2 diabetes was historically described by Jerome Conn [18] and recently confirmed in a cross-sectional metanalysis [5*]. However, it is not yet established if patients with type 2 diabetes should be systematically screened for PA or only patients with concomitant severe hypertension, in which a high prevalence was observed [19].

Finally, patients with PA have a higher risk of atrial fibrillation (AF) [5*]. No prospective studies have investigated the prevalence of PA in patients with AF; an ongoing study in patients with lone AF will provide more information in the near future [20].

Prevalence of primary aldosteronism and adrenalectomy in hospital registries

Although widely recognised as the most common cause of secondary hypertension, PA is still largely underdiagnosed. A recent survey performed among GPs from Italy and Germany, showed that ES Guidelines are only partially known and applied in clinical practice [3*]. Renin and aldosterone measurements were requested by GPs in only 7-8% of patients with hypertension [3*], in contrast with the 50% recommended by the 2016 ES Guideline [2**] and potassium levels were measured by only 43% of the GPs in Italy and 58% in Germany at diagnosis of hypertension [3*]. PA prevalence reported in patients with hypertension was 2% from German GPs and 1% from Italian GPs. Noteworthy, 36% of GPs in Italy have no patients with PA [3*].

The direct consequence of a poor knowledge and application of international guidelines is the low prevalence of PA reported by hospital registries worldwide.

If the prevalence of PA is 5% and a prevalence of hypertension among adults is 20-30%, the prevalence of PA should be 1-1.5% in the general population. However, recent analysis performed in Italy and Island showed an estimated prevalence of PA from hospital registry between 1.0-2.2/10,000 individuals [21-22]. Patients with a diagnosis of PA in an ambulatory setting and who did not undergo a subtype diagnosis with adrenal venous sampling or those who had a surgical adrenalectomy are

probably missed by this kind of registries. Nevertheless, even if we consider that patients with milder PA are probably missed, the figures reported are much lower than expected.

Hypokalaemia was present in 53-100% of patients with PA recorded in European hospital registries [22-24] and this probably reflects a selection for the most severe cases of PA and a low rate of diagnosis of milder forms. A national survey performed in Japan in 2014 demonstrated unilateral forms of PA in more than two thirds of cases [25]. Since it is known that patients with APAs display a more severe phenotype compared to patients with BAH [4*], it is probable that even in Asia, milder forms of PA are largely underdiagnosed.

Since one third of patients with PA have a unilateral form, which benefit from unilateral adrenalectomy [6*], if we consider that 1-2% of individuals in general population have a new diagnosis of hypertension each year, we would expect that the number of adrenalectomies should be 2-4/10,000 patients/year. However, the number of adrenalectomies performed for PA in an Italian Hospital registry was much lower (1.0% of expected adrenalectomies in the period 2000-2015 in the Italian region of Emilia Romagna).

Prevalence of primary aldosteronism among individuals without hypertension

Only few studies have evaluated the PA prevalence among individuals with normal blood pressure levels. The first case of PA with normotension and hypokalaemia was described in 1972 in a patient with aldosterone-producing carcinoma; subsequently, almost 30 cases of PA diagnosed in patients without hypertension have been reported in the scientific literature [26]. Hypokalaemia was the hallmark of all cases and most patients were symptomatic, female and relatively young, suggesting that age and sex may play a protective role in the hemodynamic effects mediated by aldosterone excess [27].

In 2011, Ito et al. [28] screened for PA in 44 patients with pre-hypertension and normal potassium serum level, demonstrating a relatively high prevalence of PA (6.8%). Two of the three patients with confirmed PA showed a unilateral form of PA and after unilateral adrenalectomy displayed a reduction of blood pressure levels. A recent study observed a lower prevalence of PA (1.8%) [29]. However, only 17% of patients with a positive screening test underwent a confirmatory test, suggesting that the real PA prevalence was likely higher than reported.

Other studies investigated the prevalence of aldosterone overproduction, beyond the strict criteria of PA diagnosis, identifying a prevalence of 13-14% of patients with unsuppressible aldosterone secretion [30,31]. Markou et al. used, as confirmatory test, a slightly modified version of the fludrocortisone suppression test (FST), with different cut-off criteria compared to the ES Guideline [2*] and with administration of oral dexamethasone to reduce the effect of ACTH on aldosterone secretion [30]. Instead, Baudrand et al., performed the oral sodium loading test in all patients with low plasma renin activity (PRA) levels, independent of a positive ARR at basal values [31].

Although genetic forms of PA are usually associated with a severe phenotype, in some kindreds with familial hyperaldosteronism patients with the diagnosis of PA and normotension have been reported [32-35]**.**

Renin-independent and subclinical aldosteronism

Recent developments on the pathophysiology and molecular basis of aldosterone overproduction and the study of the subclinical phase of autonomous aldosterone production, allowed the broadening of the spectrum of low-renin conditions.

Brown et al. [36*], in a prospective longitudinal study, recently demonstrated that individuals with normal blood pressure levels and suppressed renin activity, display a higher risk of developing hypertension. Furthermore, only in subjects with suppressed renin, high aldosterone levels were

associated with a higher risk of incident hypertension [36*]. These data are in agreement with the analysis of the Framingham Offspring Study that demonstrated an association between aldosterone levels and the development of hypertension in patients with normal blood pressure levels [37,38].

The progressive increase of aldosterone secretion, until its production becomes independent of renin regulation, results in normotensive aldosteronism. Patients with normotensive aldosteronism display a >15 fold higher risk of developing hypertension than controls without PA [30].

Aldosterone levels are not detrimental *per se*: in a context of sodium deficiency, high aldosterone levels are part of a homeostatic balance and do not increase the risk of aldosterone-associated cardiovascular damage. On the other hand, high aldosterone levels in the presence of high salt-diet are inappropriate and not "homeostatic", leading to higher incidence of hypertension and cardiovascular damage [5*,39].

In this context a potential significant role may be played by endogenous ouabain (EO). EO is a hormone secreted by the adrenal cortex under the regulation of adrenocortical tropic hormone (ACTH), angiotensin-II (via angiotensin receptor type 2) and sodium loading [40-42]. EO induces vasoconstriction with consequent increase of vascular resistance and blood pressure levels, and increases natriuresis [43]. When aldosterone levels are appropriately high, such as in conditions of sodium deficiency, sodium balance is preserved and EO is not increased. By contrast, when aldosterone is inappropriately high, the excessive sodium retention causes an increase of EO secretion by adrenal cortex with consequent further increase in blood pressure levels [39]. These observations explain the different predictive role of aldosterone levels observed in the study of Brown et al. In a condition of renin-independent aldosteronism the homeostatic balance is lost and the sodium load is excessive, leading to increase of EO with consequent development of hypertension. This is not the case for condition in which aldosterone is physiologically regulated by the renin-angiotensin system.

The recent description of the aldosterone-producing cell clusters (APCCs) provided a potential basis for the renin-independent aldosterone production. APCCs are clusters of subcapsular zona glomerulosa-like cells and inner zona fasciculata-like cells of 0.2-1.5 mm of diameter which express CYP11B2 (aldosterone synthase), but not CYP11B1 (11β-hydroxylase, involved in the last step of cortisol synthesis) [44,45].

Recent studies demonstrated that APCCs are relatively frequent even in the adrenal glands removed from patients with normal blood pressure levels [46]. In particular, aging is associated with a decrease in CYP11B2 expression in the normal zona glomerulosa and concomitant increase in APCCs, explaining the common finding of a progressive reduction of renin level with age and relative increase of aldosterone levels [47**]. Some APCCs harbour the same mutations associated with autonomous aldosterone production in APAs [48-50], suggesting that they could be considered as precursors of some types of APAs [51].

Conclusions

Patients with a unilateral form of PA treated with laparoscopic adrenalectomy, show a normalization or significant reduction of blood pressure levels in 84% of cases and 94% having complete biochemical cure [6*]. Patients with an absent or partial clinical response had a duration of hypertension significantly longer than cured patients [6*]. Patients with PA are at higher risk of developing cardiovascular complication and metabolic disturbances compared with patients with essential hypertension [5*]. These observations underline the importance of an early diagnosis and treatment of PA. The high prevalence of this condition, even in the general hypertensive population and in patients with a mild hypertensive phenotype, point towards the necessity of widening the number of patients with hypertension that should be screened early for PA. Unfortunately, the vast majority of patients with PA, and particularly the mildest forms, will remain undiagnosed. Therefore, although robust data from prospective randomized trials on the most appropriate treatment in patients

with low renin hypertension without a confirmed diagnosis of PA are currently lacking, the use of specific drugs that block aldosterone effects in those patients could prevent the cardio-metabolic effects of an excessive aldosterone production and should be considered in the early steps of pharmacological treatment.

Key points:

- Recent studies reported a prevalence of PA of about 6% among unselected patients with arterial hypertension, with the highest percentage in patients with the most severe degrees of hypertension, but with a not negligible rate even in patients with mild hypertension.
- Among Italian and German general practitioners, PA is investigated in less than 20% of the expected patients according to the recommendations of the ES Guideline.
- Analysis of hospital registries demonstrated unacceptably low rates of diagnosis of PA compared to the expected prevalence and even lower rates of adrenalectomies compared to the expected rate of diagnosis of unilateral forms of PA.
- The prevalence of PA among individuals with normal blood pressure levels and normokalaemia is relatively high and, among individuals with normotension, high aldosterone levels predict a high risk of developing hypertension, especially in the presence of low renin levels.

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Incidence of adrenalectomies in patients with primary aldosteronism in expert centers